

A dynamic p53-mdm2 model with delay kernel

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Abstract.

Specific activator and repressor transcription factors which bind to specific regulator DNA sequences, play an important role in gene activity control. Interactions between genes coding such transcription factors should explain the different stable or sometimes oscillatory gene activities characteristic for different tissues. In this paper, the dynamic P53-Mdm2 interaction model with distributed delays and weak kernel, is investigated. Choosing the delay or the kernel's coefficient as a bifurcation parameter, we study the direction and stability of the bifurcating periodic solutions. Some numerical examples are finally given for justifying the theoretical results.

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1. Introduction

P53 is a very important gene in oncogenesis. It is also known as "Guardian of the genome". Its anomalies are almost universal in tumoral cells [5]. The full activity of p53 gene starts when is detected a DNA damage [3,4]. These damages are mainly formed by DSB (Double-Strand Break) lesions [9]. Around these DSBs it will be formed repair complexes. These complexes include at eukaryotes the proteins: Mre11, Rad50 and NBS1 (MRN complex) and they are the signal for activation of ATM. The DSBs repair protein complexes count only for the initial activation of ATM, because the main activation is an autocatalytical process. ATM, at its own, represents the signal for activation of gene p53. Depending on the level of ATM, p53 will lead to two outcomes for the cell: one is the cell cycle arrest induced by a low level or a brief elevation of p53 protein, and the other is the apoptosis induced by a high level or a prolonged elevation of p53 protein [8]. Each of these two outcomes could not be an option for all the cells. For example, apoptosis is not accepted for neurons or myocardial muskular cells because they do not divide in adult life, so these cells will choose for cell cycle arrest. On the other hand for the enterocytes (cells of digestive tube) apoptosis is a common option, because these cells divide themselves very quickly and their lifetime is no longer than 2 days. Now is clear that should be a very good control of p53 activity in such a manner that the cell goes on right pathway (i.e. apoptosis or cell cycle arrest). This control is achieved with the help of mdm2 gene with which p53 makes a feedback loop [8, 12].

In the last years, the approaches of P53 dynamics as response to DNA damage comprise modelings in which are described three distinct subsystems: a DNA damage repair module, an ataxia telangiectasia mutated (ATM) switch and the P53-Mdm2 oscillator.

In what follows we will consider a model only for the third module. The variables of the model are: x_1 P53-mRNA concentration, x_2 Mdm2-mRNA concentration, y_1 P53-protein concentration and y_2 Mdm2-protein concentration.

We consider P53-Mdm2 model with kernel delay given by:

$$\begin{aligned}
\dot{x}_1(t) &= a_1 - a_2 x_1(t), \\
\dot{y}_1(t) &= b_1 x_1(t) - b_2 y_1(t) - b_{12} y_1(t) y_2(t), \\
\dot{x}_2(t) &= \int_0^\infty k_1(s) f(y_1(t-s)) ds - c_2 x_2(t), \\
\dot{y}_2(t) &= \int_0^\infty k_2(s) x_2(t-s) ds - d_2 y_2(t) - d_{12} y_1(t) y_2(t)
\end{aligned} \tag{1}$$

where: a_2, c_2 are the rates for mRNA degradation, b_2, d_2, b_{12}, d_{12} are the rates for proteins degradation. The function $f : \mathbb{R}_+ \rightarrow \mathbb{R}_+$, is the Hill function, given by:

$$f(x) = \frac{x^n}{a^n + x^n}$$

with $n \in \mathbb{N}^*, a > 0$. The parameters $a_1, a_2, b_1, b_2, c_2, b_{12}, d_2, d_{12}$ of the model are assumed to be positive numbers less or equal to one, the memory functions k_1, k_2 that reflect the influence of the past states on the current dynamics are a nonnegative bounded function defined on $[0, \infty)$ and

$$\int_0^\infty k_i(s) ds = 1, \quad \int_0^\infty s k_i(s) ds < \infty, \quad i = 1, 2.$$

The memory function is called delay kernel. The delay becomes a discrete one when the delay kernel is a delta function at a certain time. Usually, we employ the following form:

$$k_i(s) = \frac{q_i^{p+1}}{p!} s^p e^{-q_i s}, \quad q_i > 0, i = 1, 2, p \geq 0$$

for the memory function. When $p = 0$ and $p = 1$ the memory function are called "weak" and "strong" kernel respectively.

For $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = \delta(s - \tau_2)$, $\tau_1 \geq 0$, $\tau_2 \geq 0$ the model is given by:

$$\begin{aligned}
\dot{x}_1(t) &= a_1 - a_2 x_1(t), \\
\dot{y}_1(t) &= b_1 x_1(t) - b_2 y_1(t) - b_{12} y_1(t) y_2(t), \\
\dot{x}_2(t) &= f(y_1(t - \tau_1)) - c_2 x_2(t), \\
\dot{y}_2(t) &= x_2(t - \tau_2) - d_2 y_2(t) - d_{12} y_1(t) y_2(t).
\end{aligned} \tag{2}$$

In (2) with $\tau_1 = \tau$, $\tau_2 = 0$, $d_{12} = 0$ we obtain the model from [11] and it was studied in [10] which suggests that there is an oscillatory behavior based on observations obtained using only numerical simulations.

In present paper we will analyze the model (1) with $d_{12} = 0$ with the following initial values:

$$\begin{aligned} x_1(0) &= \bar{x}_1, y_1(\theta) = \varphi_1(\theta), \theta \in (-\infty, 0], \\ x_2(\theta) &= \varphi_2(\theta), \theta \in (-\infty, 0], y_2(0) = \bar{y}_2, \end{aligned}$$

with $\bar{x}_1 \geq 0, \bar{y}_2 \geq 0, \varphi_1(\theta) \geq 0, \varphi_2(\theta) \geq 0$, for all $\theta \in (-\infty, 0]$ and φ_1, φ_2 are differentiable functions.

Also, two delays appear in the leukopoiesis model which is analyzed in [1].

The paper is organized as follows. In section 2, we discuss the local stability for the equilibrium state of system (1), with $d_{12} = 0$, if the delay kernels k_1, k_2 are delta functions, and k_1 is delta function, k_2 is weak kernel function. We investigate the existence of the Hopf bifurcation with respect to the parameters of the delay kernels k_1, k_2 . In section 3, the direction of Hopf bifurcation is analyzed by the normal form theory and the center manifold theorem introduced by Hassard [4]. Numerical simulations for justifying the theoretical results are illustrated in section 4. Finally, some conclusions are made.

2. Local stability and the existence of the Hopf bifurcation.

We consider the model:

$$\begin{aligned} \dot{x}_1(t) &= a_1 - a_2 x_1(t), \\ \dot{y}_1(t) &= b_1 x_1(t) - b_2 y_1(t) - b_{12} y_1(t) y_2(t), \\ \dot{x}_2(t) &= \int_0^\infty k_1(s) f(y_1(t-s)) ds - c_2 x_2(t), \\ \dot{y}_2(t) &= \int_0^\infty k_2(s) x_2(t-s) ds - d_2 y_2(t). \end{aligned} \tag{3}$$

Proposition 1. *If $b_2^2 < b_1$ and $y_{10} \in (0, \frac{a_1 b_1}{a_2 b_2})$ is a solution of equation*

$$\alpha x^{n+1} - \beta x^n + \gamma x - \delta = 0$$

where

$$\alpha = a_2(b_{12} + b_2 c_2 d_2), \beta = a_1 b_1 c_2 d_2, \gamma = a_2 b_2 c_2 d_2 a^n, \delta = a_1 b_1 c_2 d_2 a^n$$

then the equilibrium point X^* of system (3) has the coordinates:

$$x_{10} = \frac{a_1}{a_2}, \quad x_{20} = d_2 y_{20}, \quad y_{20} = \frac{a_1 b_1 - a_2 b_2 y_{10}}{b_{12} y_{10} a_2}.$$

We consider the following translation:

$$x_1 = u_1 + x_{10}, y_1 = u_2 + y_{10}, x_2 = u_3 + x_{20}, y_2 = u_4 + y_{20}. \quad (4)$$

With respect to (4), system (3) can be expressed as:

$$\begin{aligned} \dot{u}_1(t) &= -a_2 u_1(t), \\ \dot{u}_2(t) &= b_1 u_1(t) - (b_2 + b_{12} y_{20}) u_2(t) - b_{12} y_{10} u_4(t) - b_{12} u_2(t) u_4(t), \\ \dot{u}_3(t) &= \int_0^\infty k_1(s) f(u_2(t-s) + y_{10}) ds - c_2(u_3(t) + x_{20}), \\ \dot{u}_4(t) &= \int_0^\infty k_2(s) u_3(t-s) ds - d_2 u_4(t). \end{aligned} \quad (5)$$

System (5) has $(0, 0, 0, 0)$ as equilibrium point.

To investigate the local stability of the equilibrium state we linearize system (5). We expand it in a Taylor series around the origin and neglect the terms of higher order than the first order for the functions from the right side of (5). We obtain:

$$\dot{U}(t) = AU(t) + B_1 U_1(t) + B_2 U_2(t), \quad (6)$$

where

$$A = \begin{pmatrix} -a_2 & 0 & 0 & 0 \\ b_1 & -(b_2 + b_{12} y_{20}) & 0 & -b_{12} y_{10} \\ 0 & 0 & -c_2 & 0 \\ 0 & 0 & 0 & -d_2 \end{pmatrix} \quad (7)$$

$$B_1 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \rho & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix} \quad (8)$$

with $\rho = f'(y_{10})$, $U(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^T$, $U_i(t) = (\int_0^\infty \rho_i(s) u_1(t -$

$s)ds, \int_0^\infty \rho_i(s)u_2(t-s)ds, \int_0^\infty \rho_i(s)u_3(t-s)ds, \int_0^\infty \rho_i(s)u_4(t-s)ds)^T, i = 1, 2.$

The characteristic equation corresponding to system (6) is $\Delta(\lambda) = 0$, where

$$\Delta(\lambda) = \det(\lambda I - A - (\int_0^\infty k_1(s)e^{-\lambda s}ds)B_1 - (\int_0^\infty k_2(s)e^{-\lambda s}ds)B_2). \quad (9)$$

From (7), (8) and (9) it results:

$$\Delta(\lambda) = (\lambda + a_2)\Delta_1(\lambda)$$

where

$$\Delta_1(\lambda) = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + r(\int_0^\infty k_1(s)e^{-\lambda s}ds)(\int_0^\infty k_2(s)e^{-\lambda s}ds) \quad (10)$$

with

$$\begin{aligned} p_2 &= b_2 + c_2 + d_2 + b_{12}y_{20}, p_1 = (c_2 + d_2)(b_2 + b_{12}y_{20}) + c_2d_2 \\ p_0 &= c_2d_2(b_2 + b_{12}y_{20}), r = \rho b_{12}y_{10}. \end{aligned} \quad (11)$$

The equilibrium point $X^* = (x_{10}, y_{10}, x_{20}, y_{20})^T$ is locally asymptotically stable if and only if all eigenvalues of $\Delta(\lambda) = 0$ have negative real parts. Because $a_2 > 0$, we will analyze the equation $\Delta_1(\lambda) = 0$. The analysis of the sign of real parts of eigenvalues is complicated and a direct approach cannot be considered.

We will analyze the eigenvalues for the equation $\Delta_1(\lambda) = 0$ if the delay kernels k_1 and k_2 are delta functions or k_1 is delta function and k_2 is weak function.

Proposition 2. *If $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = \delta(s - \tau_2)$, $\tau_1 \geq 0$, $\tau_2 \geq 0$ then:*

(i) function (10) is given by:

$$\Delta_1(\lambda, \tau) = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + re^{-\lambda\tau} \quad (12)$$

where $\tau = \tau_1 + \tau_2$.

(ii) if $\tau_1 = 0$, $\tau_2 = 0$ then the equilibrium state X^ of system (5) is locally asymptotically stable if and only if*

$$p_1p_2 > p_0 + r \quad (13)$$

where p_1, p_2, p_0, r are given by (11).

We are looking for the values τ_0 so that the equilibrium point X^* changes from local asymptotic stability to instability or vice versa. If the relation (13) holds, for $\tau > 0$ sufficiently small all roots of $\Delta_1(\lambda, \tau) = 0$ have negative real parts. The critical delay τ_0 is the smallest positive value of τ where $\Delta_1(\lambda, \tau) = 0$ has imaginary roots. Let $\lambda = \pm i\omega$ be these solutions with $\omega > 0$. Separating real and imaginary parts of $\Delta_1(i\omega, \tau) = 0$ we obtain:

$$r \cos(\omega\tau) = p_2\omega^2 - p_0, \quad r \sin(\omega\tau) = \omega p_1 - \omega^3. \quad (14)$$

A solution of (14) is a pair (ω_0, τ_0) where ω_0 is a positive root of the equation:

$$x^6 + (p_2^2 - 2p_1)x^4 + (p_1^2 - 2p_0p_2)x^2 + p_0^2 - r^2 = 0$$

and τ_0 is given by:

$$\tau_0 = \frac{1}{\omega_0} \arctg \frac{\omega_0(-p_1 + \omega_0^2)}{-p_2\omega_0^2 + p_0}.$$

From (12), we obtain:

$$\lambda' = \frac{d\lambda}{d\tau} = -\frac{\lambda r}{e^{\lambda\tau}(3\lambda^2 + 2p_2\lambda + p_1) - r\tau}. \quad (15)$$

Then, we evaluate (15) at $\lambda = i\omega_0$ and $\tau = \tau_0$ and obtain:

$$\lambda'(\tau_0) = \frac{\omega_0 r l_2}{l_1^2 + l_2^2} + i \frac{\omega_0 r l_1}{l_1^2 + l_2^2},$$

where

$$\begin{aligned} l_1 &= (p_1 - 3\omega_0^2) \cos(\omega_0\tau_0) - 2p_2\omega_0 \sin(\omega_0\tau_0) - r\tau_0 \\ l_2 &= (p_1 - 3\omega_0^2) \sin(\omega_0\tau_0) + 2p_2\omega_0 \cos(\omega_0\tau_0). \end{aligned}$$

From the above analysis and the standard Hopf bifurcation theory [4], we have the following result:

Proposition 3. *If p_1, p_2, p_0, r satisfy (13) and $p_0 < r$, for $\tau = \tau_0$, $\omega = \omega_0$ then:*

$$\operatorname{Re} \left(\frac{d\lambda}{d\tau} \right)_{\lambda=i\omega_0, \tau=\tau_0} = \frac{\omega_0 r l_2}{l_1^2 + l_2^2} \neq 0.$$

and a Hopf bifurcation occurs at the equilibrium state X^* as τ passes through τ_0 .

Proposition 4. *If $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = q_2 e^{-sq_2}$, $\tau_1 \geq 0$, $q_2 > 0$ then:
(i) function (10) is given by:*

$$\Delta_1(\lambda, \tau_1) = (\lambda + q_2)(\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0) + rq_2 e^{-\lambda\tau_1}; \quad (16)$$

(ii) if $\tau_1 = 0$, then the equilibrium state X^* of system (5) is locally asymptotically stable if and only if

$$\begin{aligned} D_2 &= (p_2 + q_2)(p_1 + q_2 p_2) - (p_0 + p_1 q_2) > 0, \\ D_3 &= (p_0 + p_1 q_2)D_2 - (p_2 + q_2)^2(q_2 p_0 + r q_2) > 0. \end{aligned} \quad (17)$$

We are looking for the values τ_{10}^* so that the equilibrium point X^* changes from local asymptotic stability to instability or vice versa. The critical delay τ_{10}^* is the smallest positive value of τ_1 where $\Delta_1(\lambda, \tau_{10}^*) = 0$ has imaginary roots. Let $\lambda = \pm i\omega$ be these solutions with $\omega > 0$. Separating real and imaginary parts of $\Delta_1(i\omega, \tau) = 0$ we obtain:

$$\begin{aligned} q_2 r \cos(\omega\tau_1) &= -\omega^4 + (p_1 + q_2 p_2)\omega^2 - q_2 p_0, \\ q_2 r \sin(\omega\tau_1) &= -(p_2 + q_2)\omega^3 + (p_0 + p_1 q_2)\omega. \end{aligned} \quad (18)$$

A solution of (18) is a pair $(\omega_{10}, \tau_{10}^*)$ where ω_{10} is a positive root of the equation:

$$x^8 + n_1 x^6 + n_2 x^4 + n_3 x^2 + n_4 = 0$$

where

$$\begin{aligned} n_1 &= (p_2 + q_2)^2 - 2(p_1 + q_2 p_2), \\ n_2 &= (p_1 + q_2 p_2)^2 + 2q_2 p_0 - 2(p_0 + p_1 q_2)(p_2 + q_2), \\ n_3 &= (p_0 + p_1 q_2)^2 - 2q_2 p_0(p_1 + q_2 p_2), \\ n_4 &= p_0^2 q_2^2 - r^2 q_2^2. \end{aligned}$$

and τ_{10}^* is given by

$$\tau_{10}^* = \frac{1}{\omega_{10}} \arctg \frac{(p_2 + q_2)\omega_{10}^3 - (p_0 + p_1 q_2)\omega_{10}}{\omega_{10}^4 - (p_1 + q_2 p_2)\omega_{10}^2 + q_2 p_0}. \quad (19)$$

From (16), we obtain:

$$\lambda' = \frac{d\lambda}{d\tau_1} = \frac{\lambda r q_2}{e^{\lambda\tau_1} (4\lambda^3 + 3(p_2 + q_2)\lambda^2 + 2(p_1 + q_2 p_2)\lambda + p_0 + p_1 q_2) - r q_2 \tau_1}. \quad (20)$$

Then, we evaluate at $\lambda = i\omega_{10}$ and $\tau_1 = \tau_{10}^*$ and obtain:

$$\lambda'(\tau_{10}^*) = -\frac{\omega_{10}r q_2 l_{20}}{l_{10}^2 + l_{20}^2}i + \frac{\omega_{10}r q_2 l_{10}}{l_{10}^2 + l_{20}^2},$$

where

$$\begin{aligned} l_{10} &= (-3(p_2 + q_2)\omega_{10}^2 + p_0 + p_1 q_2)\cos(\omega_{10}\tau_{10}) \\ &\quad + (4\omega_{10}^3 - 2(p_1 + q_2 p_2)\omega_{10})\sin(\omega_{10}\tau_{10}) - r\tau_1 q_2 \\ l_{20} &= (-3(p_2 + q_2)\omega_{10}^2 + p_0 + p_1 q_2)\sin(\omega_{10}\tau_{10}) \\ &\quad + (4\omega_{10}^3 + 2(p_1 + q_2 p_2)\omega_{10})\cos(\omega_{10}\tau_{10}). \end{aligned}$$

We have the following result:

Proposition 5. *If p_1, p_2, p_0, r, q_2 satisfy (17) for $\tau_1 = \tau_{10}^*, \omega = \omega_{10}$ then:*

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau_1}\right)_{\lambda=i\omega_{10}, \tau_1=\tau_{10}^*} = \frac{\omega_{10}r q_2 l_{10}}{l_{10}^2 + l_{20}^2} \neq 0.$$

and a Hopf bifurcation occurs at the equilibrium state X^* as τ_1 passes through τ_{10}^* .

3. Direction and stability of the Hopf bifurcation

In what follows, we will study the direction and stability in two cases: in the first case the both kernels are delta function and in the second case the kernel k_1 is delta function and the kernel k_2 is weak function.

3.1. The case $k_1(s) = \delta(s - \tau_1), k_2(s) = \delta(s - \tau_2), \tau_1 \geq 0, \tau_2 \geq 0$.

For $k_1(s) = \delta(s - \tau_1), k_2(s) = \delta(s - \tau_2), \tau_1 \geq 0, \tau_2 \geq 0$ from Proposition 2, we obtained some conditions which guarantee that system (5) undergoes Hopf bifurcation at $\tau = \tau_0$. In this section, we study the direction, the stability and the period of the bifurcating periodic solutions. The used method is based on the normal form theory and the center manifold theorem introduced by Hassard [4]. We know that if $\tau = \tau_0$ then all roots of $\Delta_1(\lambda, \tau_0) = 0$, when $\Delta_1(\lambda, \tau_0)$ is given by (12), other than $\pm i\omega_0$ have negative real parts and any roots of the form $\lambda(\tau) = \alpha(\tau) \pm i\omega(\tau)$ satisfies $\alpha(\tau_0) = 0, \omega(\tau_0) = \omega_0$ and $\frac{d\alpha(\tau_0)}{d\tau} \neq 0$.

Suppose that for given $a_1, a_2, b_1, b_2, b_{12}, c_2, a, d_2$ there is τ_0 for which $\Delta_1(\lambda, \tau_0) = 0$ exhibits a Hopf bifurcation. We consider $\tau_{10} = \tau_0 - \tau_2$, where $\tau_2 < 2\tau_0$ and $\tau_1 = \tau_{10} + \mu, \mu \in \mathbb{R}$. We regard μ as the bifurcation parameter.

For $\Phi \in C^1 = C([- \tau_1, 0], \mathbb{C}^4)$ we define a linear operator:

$$L_\mu(\Phi) = A\Phi(0) + B_1\Phi(-\tau_1) + B_2\Phi(-\tau_2)$$

where A, B_1, B_2 are given by (7), (8) and a nonlinear operator:

$$F(\mu, \Phi) = (0, -b_{12}\Phi_2(0)\Phi_1(0), \frac{1}{2}\rho_2\Phi_2^2(-\tau_1) + \frac{1}{6}\rho_3\Phi_2^3(-\tau_1), 0)^T + O(|\Phi|^4)$$

where $\Phi = (\Phi_1, \Phi_2, \Phi_3, \Phi_4)^T$, $\rho_2 = f''(y_{10})$, $\rho_3 = f'''(y_{10})$.

By the Riesz representation theorem, there exists a matrix whose components are bounded variation functions $\eta(\theta, \mu)$ with $\theta \in [-\tau_{10}, 0]$ such that

$$L_\mu\Phi = \int_{-\tau_{10}}^0 d\eta(\theta, \mu)\Phi(\theta), \quad \theta \in [-\tau_{10}, 0].$$

We can choose

$$\eta(\theta, \mu) = \begin{cases} A, & \theta = 0 \\ B_2\delta(\theta + \tau_2), & \theta \in [-\tau_2, 0) \\ B_1\delta(\theta + \tau_1), & \theta \in [-\tau_{10}, -\tau_2). \end{cases}$$

For $\Phi \in C^1$ we define:

$$\mathcal{A}(\mu)\Phi(\theta) = \begin{cases} \frac{d\Phi(\theta)}{d\theta}, & \theta \in [-\tau_{10}, 0) \\ \int_{-\tau_{10}}^0 d\eta(t, \mu)\Phi(t), & \theta = 0, \end{cases}$$

$$R(\mu)\Phi = \begin{cases} 0, & \theta \in [-\tau_{10}, 0) \\ F(\mu, \theta), & \theta = 0. \end{cases}$$

Then, we can rewrite (5) in the following vector form

$$\dot{u}_t = \mathcal{A}(\mu)u_t + R(\mu)u_t \tag{21}$$

where $u_t = u(t + \theta)$, for $\theta \in [-\tau_{10}, 0]$.

As in [4] the bifurcating periodic solutions $u(t, \mu)$ of (21) are indexed by a small parameters ε , $\varepsilon \geq 0$. The solution $u(t, \mu(\varepsilon))$ has amplitude $O(\varepsilon)$, period $T(\varepsilon)$ and nonzero Floquet exponent $\beta(\varepsilon)$ with $\beta(0) = 0$, where under our conditions μ , T and β have convergent expansions:

$$\begin{aligned}\mu &= \mu_2\varepsilon^2 + \mu_4\varepsilon^4 + \dots \\ T &= \frac{2\pi}{\omega_0}(1 + \tau_2\varepsilon^2 + \tau_4\varepsilon^4 + \dots) \\ \beta &= \beta_2\varepsilon^2 + \beta_4\varepsilon^4 + \dots\end{aligned}$$

For $\Psi \in C^1([0, \tau_{10}], \mathbb{C}^{*4})$, the adjoint operator \mathcal{A}^* of \mathcal{A} is defined as:

$$\mathcal{A}^*\Psi(s) = \begin{cases} -\frac{d\Psi(s)}{ds}, & s \in (0, \tau_{10}] \\ \int_{-\tau_{10}}^0 d\eta^T(t, 0)\Psi(-t), & s = 0. \end{cases}$$

For $\Phi \in C([- \tau_{10}, 0], \mathbb{C}^4)$ and $\Psi \in C^1([0, \tau_{10}], \mathbb{C}^{*4})$ we define the following bilinear form:

$$\langle \Psi(s), \Phi(\theta) \rangle = \bar{\Psi}(0)^T \Phi(0) - \int_{-\tau_{10}}^0 \int_{\xi=0}^{\theta} \bar{\Psi}^T(\xi - \theta) d\eta(\theta) \Phi(\xi) d\xi, \quad (22)$$

where $\eta(\theta) = \eta(\theta, 0)$.

Then, it can be verified that \mathcal{A}^* and \mathcal{A} are adjoint operators with respect to this bilinear form.

For system (21) we have:

Proposition 6. *If $\lambda_1 = i\omega_0$, $\lambda_2 = \bar{\lambda}_1$ then:*

(i) *The eigenvector of $\mathcal{A}(0)$ corresponding to λ_1 is*

$$h(\theta) = ve^{\lambda_1\theta}, \quad \theta \in [-\tau_{10}, 0]$$

where $v = (v_1, v_2, v_3, v_4)^T$,

$$v_1 = 0, v_2 = -(\lambda_1 + d_2)(\lambda_1 + c_2), v_3 = -\rho e^{\lambda_2\tau_{10}}(\lambda_1 + d_2), v_4 = -\rho e^{\lambda_2\tau_{10}},$$

$\tau_0 = \tau_{10} + \tau_{20}$.

(ii) *The eigenvector of \mathcal{A}^* corresponding to λ_2 is*

$$h^*(s) = we^{\lambda_1 s}, \quad s \in [0, \infty)$$

where $w = (w_1, w_2, w_3, w_4)^T$,

$$\begin{aligned}w_1 &= \eta, w_2 = \frac{a_2 + \lambda_2}{b_1} \eta, w_3 = -\frac{e^{\lambda_1\tau_2} b_{12} y_{10} (a_2 + \lambda_2)}{(c_2 + \lambda_2)(d_2 + \lambda_2) b_1} \eta, \\ w_4 &= -\frac{b_{12} y_{10} (a_2 + \lambda_2) e^{\lambda_1\tau_2}}{b_1 (d_2 + \lambda_2) (c_2 + d_2)} \eta\end{aligned}$$

$$\eta = \frac{a_2 + \lambda_2}{b_1} \bar{v}_2 - (\bar{v}_3 - \rho \tau_{10} e^{\lambda_1 \tau_{10}} \bar{v}_2) \frac{e^{\lambda_1 \tau_2} b_{12} y_{10} (a_2 + \lambda_2)}{(c_2 + \lambda_2)(d_2 + \lambda_2) b_1} -$$

$$-(\bar{v}_4 - \tau_2 e^{\lambda_1 \tau_2} \bar{v}_3) \frac{b_{12} y_{10} (a_2 + \lambda_2)}{b_1 (d_2 + \lambda_2)}$$

(iii) With respect to (22) we have:

$$\langle h^*, h \rangle = 1, \quad \langle h^*, \bar{h} \rangle = \langle \bar{h}^*, h \rangle = 0, \quad \langle \bar{h}^*, \bar{h} \rangle = 1.$$

Using the approach in [2], we next compute the coordinates to describe the center manifold Ω_0 at $\mu = 0$. Let $u_t = u(t + \theta)$, $\theta \in [-\tau_{10}, 0)$, be the solution of system (21) when $\mu = 0$.

We define

$$z(t) = \langle h^*, u_t \rangle, \quad w(t, \theta) = u_t(\theta) - 2\text{Re}(z(t)h(\theta)).$$

On the center manifold Ω_0 , we have:

$$w(t, \theta) = w(z(t), \bar{z}(t), \theta)$$

where

$$w(z, \bar{z}, \theta) = w_{20}(\theta) \frac{z^2}{2} + w_{11}(\theta) z \bar{z} + w_{02}(\theta) \frac{\bar{z}^2}{2} + w_{30}(\theta) \frac{z^3}{6} + \dots$$

in which z and \bar{z} are local coordinates for the center manifold Ω_0 in the direction of h^* and \bar{h}^* and $w_{02}(\theta) = \bar{w}_{20}(\theta)$.

For solution $u_t \in \Omega_0$ of equation (21), as long as $\mu = 0$, we have:

$$\dot{z}(t) = \lambda_1 z(t) + \bar{h}^*(0) F(w(z(t), \bar{z}(t), 0) + 2\text{Re}(z(t)h(0))) =$$

$$\lambda_1 z(t) + g(z, \bar{z})$$

where

$$g(z, \bar{z}) = g_{20} \frac{z^2}{2} + g_{11} z \bar{z} + g_{02} \frac{\bar{z}^2}{2} + g_{21} \frac{z^2 \bar{z}}{2} + \dots$$

Proposition 7. For the system (21) we have:

(i)

$$\begin{aligned} g_{20} &= -2b_{12}v_2v_4\bar{w}_2 + \rho_2v_2^2\bar{w}_3e^{2\lambda_2\tau_{10}}, \\ g_{11} &= -b_{12}(v_2\bar{v}_4 + \bar{v}_2v_4)\bar{w}_2 + \rho_2v_2\bar{v}_2\bar{w}_3, \\ g_{02} &= -2b_{12}\bar{v}_2\bar{v}_4\bar{w}_2 + \rho_2\bar{v}_2^2\bar{w}_3e^{2\lambda_1\tau_{10}}, \end{aligned} \tag{23}$$

(ii)

$$\begin{aligned} w_{20}(\theta) &= -\frac{g_{20}}{\lambda_1} v e^{-\lambda_1 \theta} - \frac{\bar{g}_{02}}{3\lambda_1} \bar{v} e^{\lambda_2 \theta} + E_1 e^{2\lambda_1 \theta} \\ w_{11}(\theta) &= \frac{g_{11}}{\lambda_1} v e^{\lambda_1 \theta} - \frac{\bar{g}_{11}}{\lambda_1} \bar{v} e^{\lambda_2 \theta} + E_2, \end{aligned}$$

where $E_1 = (E_{11}, E_{21}, E_{31}, E_{41})^T$ and $E_2 = (E_{12}, E_{22}, E_{32}, E_{42})^T$

$$\begin{aligned} E_{11} &= 0, E_{21} = -\frac{\rho_2 v_2^2}{\rho} + \frac{2\lambda_1 + c_2}{\rho} e^{-2\lambda_2 \tau_0} E_{41} \\ E_{31} &= (2\lambda_1 + d_2) e^{-2\lambda_2 \tau_2} E_{41} \\ E_{41} &= \frac{\rho_2 v_2^2 (2\lambda_1 + b_2 + b_{12} y_{20}) - 2b_{12} v_2 v_4 \rho}{\rho b_2 y_{10} + (2\lambda_1 + b_2 + b_{12} y_{20})(2\lambda_1 + c_2) e^{-2\lambda_2 \tau_0}} \\ E_{12} &= 0, E_{22} = -\frac{\rho_2 v_2 \bar{v}_2}{\rho} + \frac{c_2 d_2}{\rho} E_2^4, E_{32} = d_2 E_2^4 \\ E_{42} &= \frac{\rho b_{12} (v_2 \bar{v}_4 + \bar{v}_2 v_4) - \rho_2 v_2 \bar{v}_2 (b_2 + b_{12} y_{20})}{(b_2 + b_{12} y_{20}) c_2 d_2 + \rho b_2 y_{10}}. \end{aligned}$$

(iii)

$$\begin{aligned} g_{21} &= -3b_{12}(\bar{v}_2 w_{420}(0) + 2v_2 w_{411}(0) + \bar{v}_4 w_{220}(0) + 2w_{211}(0)v_4)\bar{w}_2 + \\ &+ \bar{w}_3[6\rho_2(2v_2 e^{\lambda_2 \tau_1} - w_{211}(-\tau_1) + 6\bar{v}_2 e^{\lambda_1 \tau_1} w_{220}(-\tau_1)) + 3\rho_3 v_2^2 e^{2\lambda_2 \tau_1} \bar{v}_2 e^{\lambda_1 \tau_1}], \end{aligned} \quad (24)$$

with $w_{20}(\theta) = (w_{120}(\theta), w_{220}(\theta), w_{320}(\theta), w_{420}(\theta))^T$ and $w_{11}(\theta) = (w_{111}(\theta), w_{211}(\theta), w_{311}(\theta), w_{411}(\theta))^T$

Based on the above analysis and calculation, we can see that each g_{ij} in (23), (24) are determined by the parameters and delay from system (21). Thus, we can explicitly compute the following quantities:

$$\begin{aligned} C_1(0) &= \frac{i}{2\omega_0} (g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2} \\ \mu_2 &= -\frac{Re(C_1(0))}{Re\lambda'(0)}, T_2 = -\frac{Im(C_1(0)) + \mu_2 Im\lambda'(0)}{\omega_0}, \beta_2 = 2Re(C_1(0)), \end{aligned} \quad (25)$$

where $\lambda'(0)$ is given by

$$\lambda'(0) = \left(\frac{r}{e^{\lambda\tau}(3\lambda^2 + 2p_2\lambda + p_1 - r)} \right)_{\lambda=i\omega_0, \tau=\tau_0}.$$

In summary, this leads to the following result:

Theorem 1. *In formulas (25), μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0 (< 0)$, then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_0 (< \tau_0)$; β_2 determines the stability of the bifurcating periodic solutions: the solutions are orbitally stable (unstable) if $\beta_2 < 0 (> 0)$; and T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0 (< 0)$.*

3.2. The case $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = q_2 e^{-q_2 s}$, $\tau_1 \geq 0$, $q_2 > 0$.

For $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = q_2 e^{-q_2 s}$, $\tau_1 \geq 0$, $q_2 > 0$, system (5) is given by:

$$\begin{aligned} \dot{u}_1(t) &= -a_2 u_1(t), \\ \dot{u}_2(t) &= b_1 u_1(t) - (b_2 + b_{12} y_{20}) u_2(t) - b_{12} y_{10} u_4(t) - b_{12} u_2(t) u_4(t), \\ \dot{u}_3(t) &= f(u_2(t - \tau_1) + y_{10}) - c_2(u_3(t) + x_{20}), \\ \dot{u}_4(t) &= u_5(t) - d_2 u_4(t), \\ \dot{u}_5(t) &= q_2(u_3(t) - u_5(t)). \end{aligned} \tag{26}$$

We expand it in a Taylor series around the origin and neglect the terms of higher order than the first order for the functions from the right side of (26). We obtain:

$$\dot{U}(t) = A_{12} U(t) + B_{12} U(t - \tau_1),$$

where

$$A_{12} = \begin{pmatrix} -a_2 & 0 & 0 & 0 & 0 \\ b_1 & -(b_2 + b_{12} y_{20}) & 0 & -b_{12} y_{10} & 0 \\ 0 & 0 & -c_2 & 0 & 0 \\ 0 & 0 & 0 & -d_2 & 1 \\ 0 & 0 & q_2 & 0 & -q_2 \end{pmatrix} \tag{27}$$

$$B_{12} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \rho & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{28}$$

with $U(t) = (u_1(t), u_2(t), u_3(t), u_4(t), u_5(t))$, $U(t - \tau_1) = (u_1(t - \tau_1), u_2(t - \tau_1), u_3(t - \tau_1), u_4(t - \tau_1), u_5(t - \tau_1))^T$.

Let τ_{10}^* given by (19) and $\tau_1 = \tau_{10}^* + \mu$, $\mu \in \mathbb{R}$. We regard μ as the bifurcation parameter.

For $\Phi \in C^1 = C^1([-\tau_1, 0], \mathbb{C}^5)$ we define a linear operator:

$$L_{12\mu}(\Phi) = A_{12}\Phi(0) + B_{12}\Phi(-\tau_1)$$

where A_{12}, B_{12} are given by (27), (28) and a nonlinear operator:

$$F_{12}(\mu, \Phi) = (0, -b_{12}\Phi_2(0)\Phi_1(0), \frac{1}{2}\rho_2\Phi_2^2(-\tau_1) + \frac{1}{6}\rho_3\Phi_2^3(-\tau_1), 0, 0)^T + O(|u|^4)$$

where $\Phi = (\Phi_1, \Phi_2, \Phi_3, \Phi_4, \Phi_5)^T$, $\rho_2 = f''(y_{10})$, $\rho_3 = f'''(y_{10})$.

By the Riesz representation theorem, there exists a matrix whose components are bounded variation functions $\eta(\theta, \mu)$ with $\theta \in [-\tau_{10}^*, 0]$ such that

$$L_{12\mu}\Phi = \int_{-\tau_{10}^*}^0 d\eta(\theta, \mu)\Phi(\theta), \quad \theta \in [-\tau_{10}^*, 0].$$

We can choose

$$\eta_{12}(\theta, \mu) = \begin{cases} A_{12}, & \theta = 0 \\ B_{12}\delta(\theta + \tau_1), & \theta \in [-\tau_{10}^*, 0). \end{cases}$$

For $\Phi \in C^1$ we define:

$$\mathcal{A}_{12}(\mu)\Phi = \begin{cases} \frac{d\Phi(\theta)}{d\theta}, & \theta \in [-\tau_{10}^*, 0) \\ \int_{-\tau_{10}^*}^0 d\eta_{12}(t, \mu)\Phi(t), & \theta = 0, \end{cases}$$

$$R_{12}(\mu)\Phi = \begin{cases} 0, & \theta \in [-\tau_{10}^*, 0) \\ F_{12}(\mu, \theta), & \theta = 0. \end{cases}$$

Then, we can rewrite (26) in the following vector form

$$\dot{u}_t = \mathcal{A}_{12}(\mu)u_t + R_{12}(\mu)u_t \tag{29}$$

where $u_t = u(t + \theta)$, for $\theta \in [-\tau_{10}^*, 0]$.

For $\Psi \in C^1([0, \tau_{10}^*], \mathbb{C}^{*5})$, the adjoint operator \mathcal{A}_{12}^* of \mathcal{A} is defined as:

$$\mathcal{A}_{12}^* \Psi(s) = \begin{cases} -\frac{d\Psi(s)}{ds}, & s \in (0, \tau_{10}^*] \\ \int_{-\tau_{10}^*}^0 d\eta^T(t, 0) \Psi(-t), & s = 0. \end{cases}$$

For $\Phi \in C([- \tau_{10}^*, 0], \mathbb{C}^5)$ and $\Psi \in C^1([0, \tau_{10}^*], \mathbb{C}^{*5})$ we define the following bilinear form:

$$\langle \Psi(s), \Phi(\theta) \rangle = \bar{\Psi}(0)^T \Phi(0) - \int_{-\tau_{10}^*}^0 \int_{\xi=0}^{\theta} \bar{\Psi}^T(\xi - \theta) d\eta_{12}(\theta) \Phi(\xi) d\xi, \quad (30)$$

where $\eta(\theta) = \eta(\theta, 0)$.

Then, it can be verified that \mathcal{A}_{12}^* and \mathcal{A}_{12} are adjoint operators with respect to this bilinear form.

For system (29) we have:

Proposition 8. *If $\lambda_1 = i\omega_{10}$, $\lambda_2 = \bar{\lambda}_1$ then:*

(i) *The eigenvector of $\mathcal{A}_{12}(0)$ corresponding to λ_1 is*

$$h(\theta) = v e^{\lambda_1 \theta}, \quad \theta \in [-\tau_{10}^*, 0]$$

where $v = (v_1, v_2, v_3, v_4, v_5)^T$,

$$v_1 = 0, v_2 = \frac{(\lambda_1 + q_2)(\lambda_1 + c_2)}{\rho_1} e^{\lambda_1 \tau_1}, v_3 = \lambda_1 + q_2, v_4 = \frac{q_2}{\lambda_1 + d_2}, v_5 = q_2.$$

(ii) *The eigenvector of \mathcal{A}_{12}^* corresponding to λ_2 is*

$$h^*(s) = w e^{\lambda_1 s}, \quad s \in [0, \infty)$$

where $w = (w_1, w_2, w_3, w_4, w_5)^T$,

$$\begin{aligned} w_1 &= \frac{b_1}{(\lambda_2 + a_2)\eta}, w_2 = \frac{1}{\eta}, w_3 = -\frac{q_2 b_{12} y_{10}}{(c_2 + \lambda_2)(d_2 + \lambda_2)(q_2 + \lambda_2)\eta}, \\ w_4 &= -\frac{b_{12} y_{10}}{(d_2 + \lambda_2)\eta}, w_5 = -\frac{b_{12} y_{10}}{(d_2 + \lambda_2)(q_2 + \lambda_2)\eta} \\ \eta &= \bar{v}_2 - \frac{q_2 b_{12} y_{10}}{(c_2 + \lambda_2)(d_2 + \lambda_2)(q_2 + \lambda_2)} \bar{v}_3 - \frac{b_{12} y_{10}}{(d_2 + \lambda_2)} \bar{v}_4 - \frac{b_{12} y_{10}}{(d_2 + \lambda_2)(q_2 + \lambda_2)} \bar{v}_5 \\ &\quad - \frac{\rho_1 q_2 b_{12} y_{10}}{(c_2 + \lambda_2)(d_2 + \lambda_2)(q_2 + \lambda_2)\lambda_2^2} (e^{\lambda_1 \tau_{10}^*} - \tau_{10}^* \lambda_2 e^{\lambda_1 \tau_{10}^*} - 1) \bar{v}_2. \end{aligned}$$

(iii) With respect to (20) we have:

$$\langle h^*, h \rangle = 1, \quad \langle h^*, \bar{h} \rangle = \langle \bar{h}^*, h \rangle = 0, \quad \langle \bar{h}^*, \bar{h} \rangle = 1.$$

Using the approach in [2], we next compute the coordinates to describe the center manifold Ω_0 at $\mu = 0$. Let $u_t = u(t + \theta)$, $\theta \in [-\tau_{10}^*, 0)$, be the solution of system (29) when $\mu = 0$.

We define

$$z(t) = \langle h^*, u_t \rangle, \quad w(t, \theta) = u_t(\theta) - 2\text{Re}(z(t)h(\theta)).$$

On the center manifold Ω_0 , we have:

$$w(t, \theta) = w(z(t), \bar{z}(t), \theta)$$

where

$$w(z, \bar{z}, \theta) = w_{20}(\theta) \frac{z^2}{2} + w_{11}(\theta) z \bar{z} + w_{02}(\theta) \frac{\bar{z}^2}{2} + w_{30}(\theta) \frac{z^3}{6} + \dots$$

in which z and \bar{z} are local coordinates for the center manifold Ω_0 in the direction of h^* and \bar{h}^* and $w_{02}(\theta) = \bar{w}_{20}(\theta)$.

For solution $u_t \in \Omega_0$ of equation (29), as long as $\mu = 0$, we have:

$$\begin{aligned} \dot{z}(t) &= \lambda_1 z(t) + \bar{h}^*(0) F(w(z(t), \bar{z}(t), 0) + 2\text{Re}(z(t)h(0))) = \\ &= \lambda_1 z(t) + g(z, \bar{z}) \end{aligned}$$

where

$$g(z, \bar{z}) = g_{20} \frac{z^2}{2} + g_{11} z \bar{z} + g_{02} \frac{\bar{z}^2}{2} + g_{21} \frac{z^2 \bar{z}}{2} + \dots$$

Proposition 9. For the system (29) we have:

(i)

$$\begin{aligned} g_{20} &= -2b_{12}v_2v_4\bar{w}_2 + \rho_2v_2^2\bar{w}_3e^{2\lambda_2\tau_{10}^*}, \\ g_{11} &= -b_{12}(v_2\bar{v}_4 + \bar{v}_2v_4)\bar{w}_2 + \rho_2v_2\bar{v}_2\bar{w}_3, \\ g_{02} &= -2b_{12}\bar{v}_2\bar{v}_4\bar{w}_2 + \rho_2\bar{v}_2^2\bar{w}_3e^{2\lambda_1\tau_{10}^*}, \end{aligned} \tag{31}$$

(ii)

$$\begin{aligned} w_{20}(\theta) &= -\frac{g_{20}}{\lambda_1} v e^{-\lambda_1 \theta} - \frac{\bar{g}_{02}}{3\lambda_1} \bar{v} e^{\lambda_2 \theta} + E_1 e^{2\lambda_1 \theta} \\ w_{11}(\theta) &= \frac{g_{11}}{\lambda_1} v e^{\lambda_1 \theta} - \frac{\bar{g}_{11}}{\lambda_1} \bar{v} e^{\lambda_2 \theta} + E_2, \end{aligned}$$

where $E_1 = (E_{11}, E_{21}, E_{31}, E_{41}, E_{51})^T$ and $E_2 = (E_{12}, E_{22}, E_{32}, E_{42}, E_{52})^T$

$$\begin{aligned}
E_{11} &= 0, E_{21} = \frac{a_{22}F_{220} - a_{12}F_{320}}{a_{11}a_{22} + a_{12}a_{21}}, E_{31} = \frac{q_2 + 2\lambda_1}{q_2}E_{51}, \\
E_{41} &= \frac{1}{d_2 + 2\lambda_1}E_{51}, E_{51} = \frac{a_{21}F_{220} + a_{11}F_{320}}{a_{11}a_{22} + a_{12}a_{21}} \\
a_{11} &= 2\lambda_1 + b_2 + b_{12}y_{10}, \quad a_{12} = \frac{b_{12}y_{10}}{d_2 + 2\lambda_1}, \\
a_{21} &= \rho_1 e^{2\lambda_2\tau_{10}^*}, \quad a_{22} = \frac{(c_2 + 2\lambda_1)(q_2 + 2\lambda_1)}{q_2}, \\
F_{220} &= -2b_{12}v_2v_4, F_{320} = \rho_2v_2^2e^{2\lambda_2\tau_{10}^*}, \\
E_{12} &= 0, E_{22} = \frac{c_{22}F_{211} - c_{12}F_{311}}{c_{11}c_{22} + c_{12}c_{21}}, E_{32} = E_{52}, E_{42} = \frac{1}{d_2}E_{52}, \\
E_{52} &= \frac{c_{21}F_{211} + c_{11}F_{311}}{c_{11}c_{22} + c_{12}c_{21}} \\
c_{11} &= b_2 + b_{12}y_{20}, c_{12} = b_{12}y_{10}, c_{21} = \rho_1, c_{22} = c_2 \\
F_{211} &= -b_{12}(v_2\bar{v}_4 + \bar{v}_2v_4), F_{311} = v_2\bar{v}_2\rho_2.
\end{aligned}$$

(iii)

$$\begin{aligned}
g_{21} &= -3b_{12}(\bar{v}_2w_{420}(0) + 2v_2w_{411}(0) + \bar{v}_4w_{220}(0) + 2w_{211}(0)v_4)\bar{w}_2 + \\
&+ \bar{w}_3[6\rho_2(2v_2e^{\lambda_2\tau_{10}^*} - w_{211}(-\tau_{10}^*) + 6\bar{v}_2e^{\lambda_1\tau_{10}^*}w_{220}(-\tau_{10}^*)) + 3\rho_3v_2^2e^{2\lambda_2\tau_{10}^*}\bar{v}_2e^{\lambda_1\tau_{10}^*}],
\end{aligned} \tag{32}$$

with $w_{20}(\theta) = (w_{120}(\theta), w_{220}(\theta), w_{320}(\theta), w_{420}(\theta), w_{520}(\theta))$ and $w_{11}(\theta) = (w_{111}(\theta), w_{211}(\theta), w_{311}(\theta), w_{411}(\theta), w_{511}(\theta))$, $\theta \in [-\tau_{10}^*, 0]$.

Based on the above analysis and calculation, we can see that each g_{ij} in (31), (32) are determined by the parameters and delay from system (26). Thus, we can explicitly compute the following quantities:

$$\begin{aligned}
C_1(0) &= \frac{i}{2\omega_{10}}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2} \\
\mu_2 &= -\frac{Re(C_1(0))}{Re\lambda'(0)}, T_2 = -\frac{Im(C_1(0)) + \mu_2Im\lambda'(0)}{\omega_{10}}, \beta_2 = 2Re(C_1(0)),
\end{aligned} \tag{33}$$

where $\lambda'(0)$ is given by

$$\lambda'(0) = \left(\frac{\lambda r q_2}{e^{\lambda \tau_1} (4\lambda^3 + 3(p_2 + q_2)\lambda^2 + 2(p_1 + q_2 p_2)\lambda + p_0 + p_1 q_2) - r q_2 \tau_1} \right)_{\lambda=i\omega_{10}, \tau_1=\tau_{10}^*}.$$

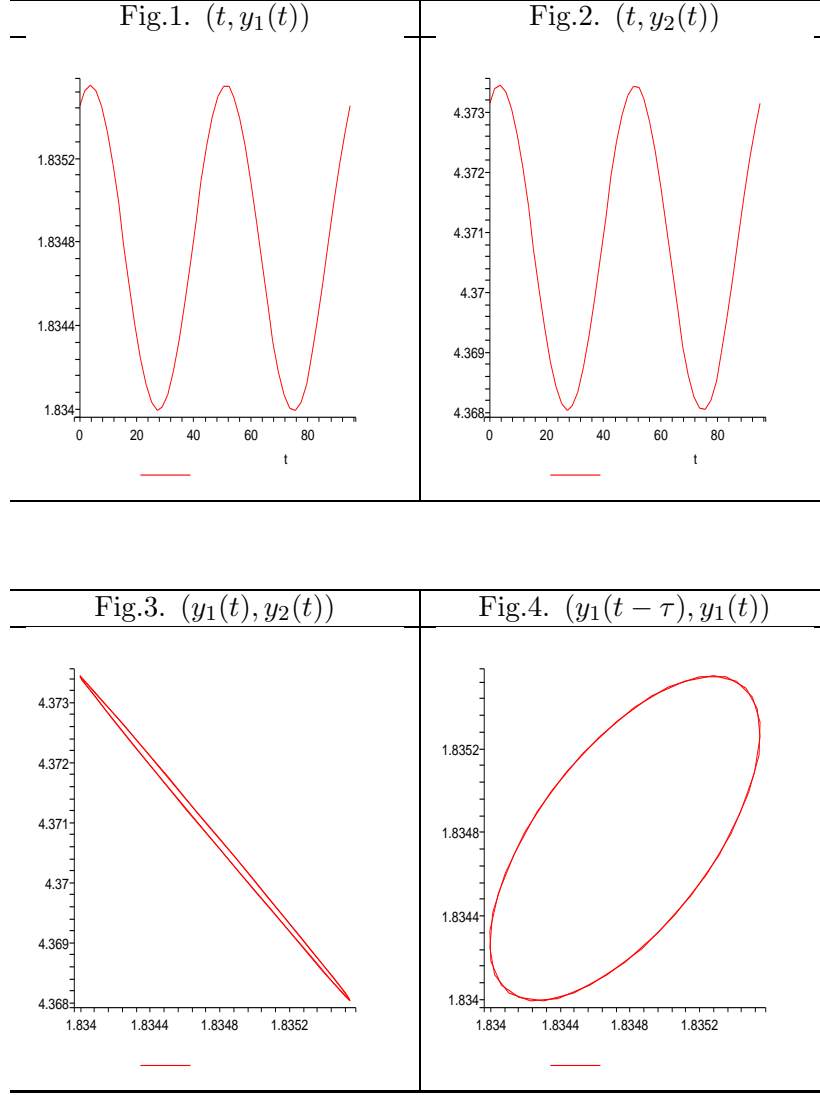
We have:

Theorem 2. *In formulas (33), μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0 (< 0)$, then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau_1 > \tau_{10}^* (< \tau_{10}^*)$; β_2 determines the stability of the bifurcating periodic solutions: the solutions are orbitally stable (unstable) if $\beta_2 < 0 (> 0)$; and T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0 (< 0)$.*

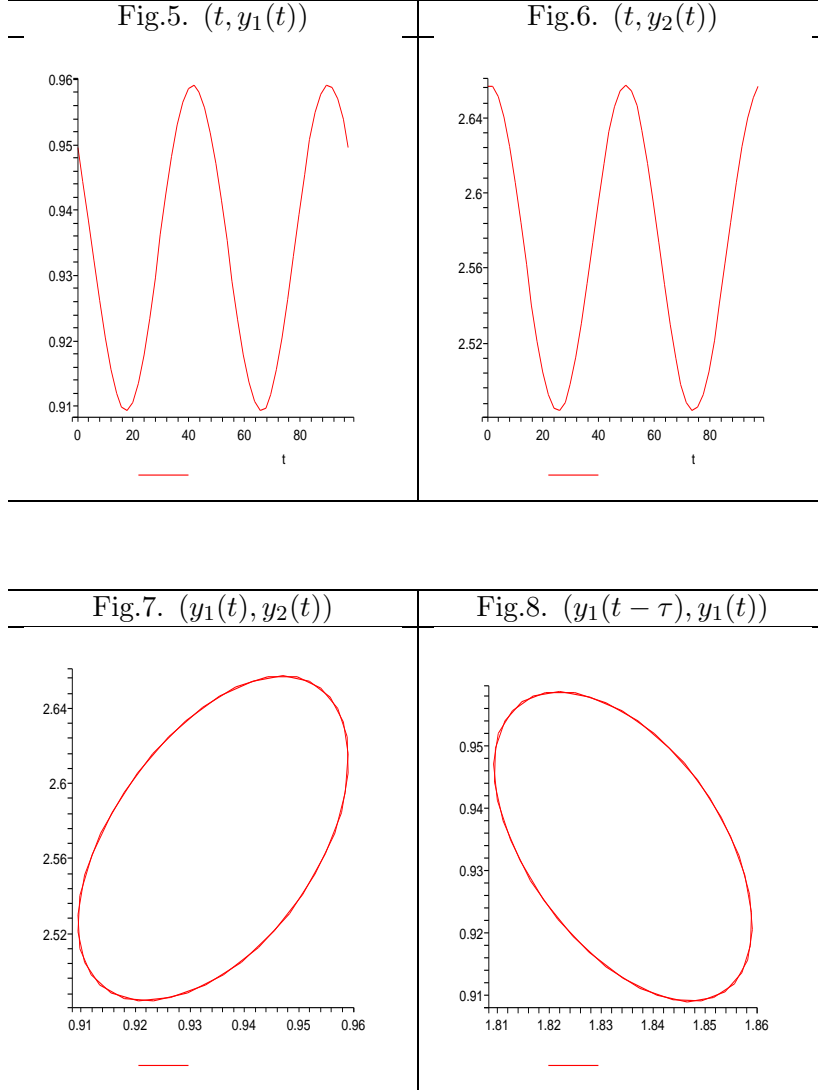
4. Numerical examples.

For the numerical simulations we use Maple 9.5. In this section, we consider system (6) with $a_1 = 2, a_2 = 0.55, b_1 = 1, b_2 = 0.8, c_2 = 0.1, b_{12} = 1.5, d_2 = 0.1, a = 4, n = 2$. We obtain: $x_{10} = 3.636363636, y_{10} = 0.8347719895, y_{20} = 2.370744013, x_{20} = 0.2370744013$.

In the first case, $k_1(s) = \delta(s - \tau_1), k_2(s) = \delta(s - \tau_2)$, for $\tau_2 = 3$, we have: $\omega_{10} = 0.1324013896, \mu_2 = -0.4204703301, \beta_2 = 0.2799153884, T_2 = 0.0005051758260, \tau_0 = 9.541873607$. Then the Hopf bifurcation is subcritical and the bifurcating periodic solutions exist for $\tau > \tau_0$; the solutions are orbitally unstable and the period of the solution is increasing. The waveforms are displayed in Fig1 and Fig2 and the phase plane diagrams of the state variables $y_1(t), y_2(t)$ and $y_1(t - \tau), y_1(t)$ are displayed in Fig3 and Fig4:



In the second case, $k_1(s) = \delta(s - \tau_1)$, $k_2(s) = q_2 e^{-q_2 s}$ for $q_2 = 0.5$, we have: $\omega_{10} = 0.1290621026$, $\mu_2 = -0.5993860816$, $\beta_2 = -0.7476750590$, $T_2 = 0.1798944390$, $\tau_{10}^* = 32.37014890$. Then the Hopf bifurcation is subcritical and the bifurcating periodic solutions exist for $\tau_1 > \tau_{10}^*$; the solutions are orbitally stable and the period of the solution is increasing. The waveforms are displayed in Fig5 and Fig6 and the phase plane diagrams of the state variables $y_1(t)$, $y_2(t)$ and $y_1(t - \tau)$, $y_1(t)$ are displayed in Fig7 and Fig8:



5. Conclusions.

As in our previous models [11,13], we obtain an oscillatory behavior similar to that observed experimentally [5]. The conclusion is not surprising, but is useful as this model provides a more accurate approach of the interaction P53-Mdm2.

The improvements of the model from [11] done in the present paper, proved usefulness as we obtained a smoother modelling of the phenomenon and the oscillating behavior remained which as similar with that from [5].

Using the method from this paper, we will do a qualitative analysis of the model from [9] in our future papers.

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